PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CZ2004/000085	14.12.2004	16.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07D491/22

Applicant
PLIVA-LACHEMA A.S.

1. This opinion contains indications relating to the following items:

   - ☒ Box No. I Basis of the opinion
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

   If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

   If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

   For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CZ2004/000085

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/CZ2004/000085

Section V:

1. The application relates to a process for the preparation of 7-ethyl-10-hydroxycamptothecin. The process makes use of the ring A activation by providing a hydrogenated pyridine ring B and subsequent oxidation.

   The relevant prior art has been indicated in the search report.

   D1: WOOD J L ET AL: "An Efficient Conversion of Camtothecin to 10-Hydroxycamptothecin" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 60, 1995, pages 5739-5740, XP002323603 ISSN: 0022-3263
   D2: US-A-4 473 692 (MIYASAKA ET AL) 25 September 1984 (1984-09-25)
   D3: US-A-5 734 056 (BURK ET AL) 31 March 1998 (1998-03-31)

2. The processes disclosed in D1, D2 and D3 are analogous to the presently claimed synthesis method and differ merely in the absence of the alkyl group at position 7. Hence, the claimed subject-matter appears to be novel in the sense of Art. 33(2) PCT.

3. D1 is considered to be the closest prior art. It teaches (cf. page 5739, right hand side and page 5740) the general synthesis strategy for 10-hydroxy substituted camptothecin derivatives by activating this position first through the reduction of the pyridine ring B, and then by oxidizing rings A and B. On the pending paragraph between the pages 5739 and 5740, it is taught, that only particular oxidant-solvent combination are technically useful, as a series of alternative oxidants, either lacked regioselectivity to the ring position 10, or further oxidised the desired end product. "The key turned out to be conducting the oxidation in a solvent mixture consisting of water and a miscible organic solvent. Among several systems that gave good results, 1:1 acetic acid/water provided the highest yiel and selectivity ... With iodobenzene diacetate as the oxidant, 2 was typically isolated in 88-91% yield". D2 uses also the activation strategy taught by D1, namely the reduction of the pyridine B ring with subsequent introduction of substituents at the 10 position in ring A (cf. column 9). The skilled person will notice, that the presence or absence of a substituent at position 7

in the pyridine ring, is of no relevance for this synthesis strategy. By consequence, the skilled person, who was looking to solve the problem of providing an alternative method for the production 7-ethyl-10-hydroxycamptothecin, would have use the method of D1 in plain analogy with a reasonable expectation of success. The presently suggested use of the iodobenzene diacetate/water/acetic acid system is therefore considered to represent an obvious solution, which does not involve an inventive step.

In the light of the problems mentioned in D1 (cf. the discussion and the cited passages above), the present application does not contain credible evidence, that oxidants other than hypervalent iodine compounds, also do solve the stated problem. In particular, the claimed use of peroxodisulfate and periodate oxidants have is not supported by experiments. While this type of oxidants has also been suggested in D3 (cf. column 11, paragraph 1), no experimental verification has been provided. The present claims, which embrace such oxidants, are therefore considered speculative and do not credibly solve the stated problem. By consequence, they do not meet the requirements of Art. 33(3) PCT.

Section VI:

1. The international application D4 (= WO 2004/100897 A, SCINOPHARM TAIWAN, LTD, 25 November 2004) discloses in the examples on pages 6 and 7 the process of the present application. Since, however, D4 has been published between the priority and filing date of the present application, this document does not form part of the state of the art as defined by the PCT. By consequence, D4 has been disregarded from further consideration, but will become relevant in the regional phase before the EPO.

Section VIII:

1. The closest prior, which is considered essential for the understanding of the present application, has not been mentioned in the description.